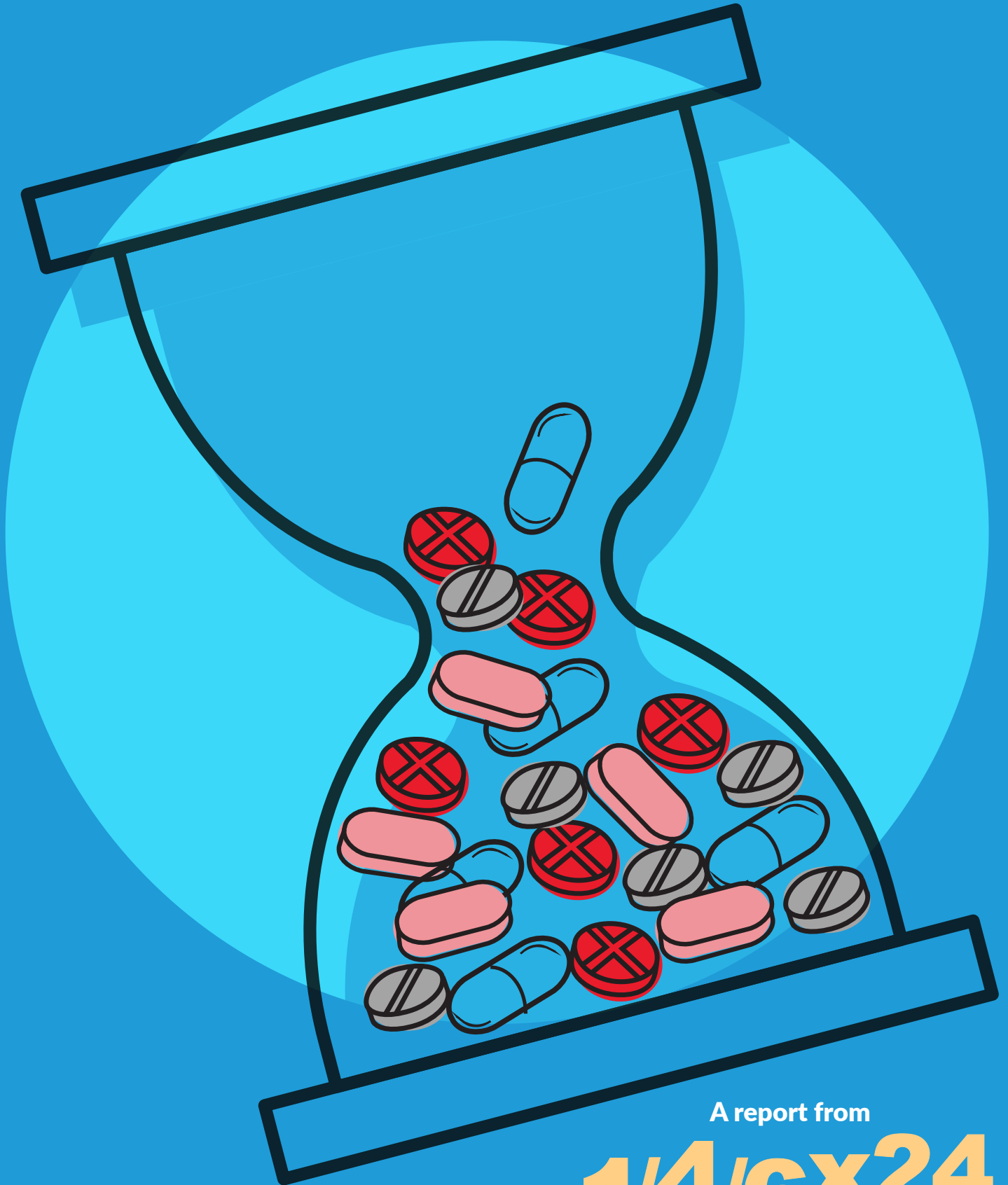


# Getting Better Faster

Delivering on the Promise of New TB Treatments



A report from

**1/4/6x24**

A Campaign to Rally  
Energy, Political Will  
& Funding to End TB

**This publication is dedicated to Dr Paul Farmer, a visionary physician and health advocate who battled on many fronts to bring the best medical care to some of the world's most malignly neglected people and in some of the world's most underserved settings. He would be both amazed by the innovations available to improve the lives of people impacted by TB and horrified by how little access most people have to the latest TB diagnostic, treatment, and preventive measures. Paul would have been a fierce supporter of the 1/4/6x24 Campaign and its commitment to realizing the human rights to health and science.**

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# Getting Better Faster

## Delivering on the Promise of New TB Treatments

A report from the 1/4/6x24 Campaign

March 2024

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### Introduction

For millennia, a central impediment in the fight against tuberculosis (TB) was an *absence* of effective, humane therapeutics. Thanks to 20 years of renewed investments in TB drug development and research, such therapeutic options now exist: **1**-month or once-weekly regimens to prevent TB; **4**-month regimens to treat drug-susceptible TB; and **6**-month regimens to treat drug-resistant TB. Today, the challenge is *access* to these long-awaited shorter, safer TB treatment and prevention regimens.

The 1/4/6x24 Campaign was launched mid-2022 with the ambition of ensuring that, by the end of **2024**, everyone who needs them has access to the best TB therapeutics available.

The Campaign is grounded in the recognition that the fulfilment of the right to health is inextricably linked to the right to enjoy and share in the benefits of scientific progress and its applications – known as the right to science. This was the ethic that fueled the life's work of the late Dr Paul Farmer, and it was his legacy that inspired the Campaign.

Historic reductions in the cost of bedaquiline, pretomanid, rifapentine, and rapid molecular diagnostics will undoubtedly hasten the uptake of the new regimens, but affordability is only one component of access. Full scale-up of the 1/4/6 regimens demands adequately resourced TB programs and health systems, updated national policies, and the widespread availability of diagnostics in the public and private sectors. This enabling infrastructure – also championed by Farmer as the '5 Ss': staff, stuff, space, systems, and support – is needed to fully realize the benefits of the right to science and the potential of the 1/4/6 regimens.

The Campaign is led by a coalition of TB survivors, researchers, clinicians, activists, and civil society professionals representing 21 organizations (see annex 1). Its success to date is the direct result of the responsiveness and action of affected community members and other organizations. In particular, the Stop TB Partnership, the O'Neill Institute, and the Global Fund Advocates Network (GFAN) played an instrumental role in supporting TB advocates to quickly and effectively push for the inclusion of the 1/4/6 regimens in countries' funding requests to the Global Fund to Fight AIDS, TB and Malaria (Global Fund) for the 2023-2025 grant cycle.

This report aims to assess scale-up of the 1/4/6 regimens at the midpoint of the Campaign, drawing on, among other sources, data from funding requests submitted to the Global Fund (see annexes 2 and 3). The report showcases countries' successes in scaling up these regimens, draws attention to the remaining gaps, and charts a course of action for countries and global stakeholders to meet the Campaign goals by the end of 2024.

FIGURE 1

# Timeline of research to policy translation for the 1/4/6 regimens

## Research results

**July 2011**  
Soweto 3HP trial established 3HP as an effective regimen

**December 2011**  
PREVENT TB showed 3HP was as effective as 9H in preventing TB

**March 2019**  
BRIEF TB/A5279 showed 1HP was noninferior to 9H for preventing TB in PLHIV

**March 2020**  
Nix-TB showed 6BPaL was effective in treating people with highly drug-resistant TB

**May 2021**  
Study 31/A5349 showed 4HPMZ was noninferior to the standard six-month regimen

**March 2022**  
SHINE showed that 4HRZE was noninferior to 6HRZE in children with drug-susceptible, nonsevere, smear-negative TB

**September 2022**  
ZeNix showed that 6BPaL with a linezolid dose of 600 mg maintains high efficacy and leads to fewer adverse events

**December 2022**  
TB-PRACTECAL showed much-improved treatment success rates with the 6BPaL[M] compared with standard-of-care regimens

## Policy changes

2011-13

2014-18

2019

2020

2021

2022

**February 2020**  
WHO recommends use of 1HP and 3HP

**June 2020**  
WHO recommends BPaL under operational research conditions

**June 2021**  
WHO issues rapid communication endorsing programmatic use of 4HPMZ

**August 2021**  
WHO issues rapid communication endorsing programmatic use of 4HRZE in children with nonsevere TB

**May 2022**  
WHO issues rapid communication endorsing programmatic use of 6BPaL[M]

**March 2022**  
WHO recommends four-month HRZE regimen for children with nonsevere TB

**May 2022**  
WHO recommends four-month HPMZ regimen for adults and adolescents with drug-susceptible TB

**December 2022**  
WHO recommends 6BPaL[M] for drug-resistant TB

## Key recent price reductions

**Bedaquiline:** 55% price reduction, from \$289 to \$130 per six-month treatment course, and a commitment from Johnson & Johnson not to enforce secondary patents on bedaquiline for drug-resistant TB in low- and middle-income countries

**Pretomanid:** 34% price reduction, from \$364 to \$240 per six-month treatment course

**3HP:** 30% price reduction, from \$14.25 to \$9.99 per preventive treatment course, alongside a pledge of \$25 million from USAID and PEPFAR to support 3HP scale-up to reach an additional 2.5 million people at risk for TB

**Xpert MTB/RIF Ultra:** 20% price reduction, from \$9.98 to \$7.97 per test for TB and rifampicin resistance

**Truenat MTB and MTB Plus:** 12% price reduction, from \$9 to \$7.90 per test for TB and rifampicin resistance

## Key campaign moments

**July 2022**  
The 1/4/6x24 Campaign is launched by TAG, PIH, and MSF at the AIDS 2022 Conference in Montreal

**July 2022**  
Global Fund includes 1/4/6 regimens as program essentials in its Information Note for TB

**October 2022**  
USAID hosts 1/4/6x24 Campaign Call-to-Action at its TB Symposium in Washington, DC. Key global health actors made commitments to the campaign

**November 2022**  
GFAN publishes advocacy guides to support inclusion of 1/4/6 regimens in national strategic plans and Global Fund funding requests

**January 2023**  
TAG publishes Community Campaign Training Materials for the 1/4/6x24 Campaign.

**September 2023**  
Member states adopt a political declaration at the United Nations High-Level Meeting on TB recognizing the right to science and the need to scale up access to shorter, safer TB regimens

## Deadlines

**December 2024**  
Deadline to meet the goals of the 1/4/6x24 Campaign

**September 2027**  
Deadline for countries to meet funding and implementation commitments made at the 2023 United Nations High-Level Meeting on TB

**1** The "1" preventive treatment regimens

**4** The "4" drug-susceptible treatment regimens

**6** The "6" drug-resistant treatment regimens





## The “1”: preventive treatment

The short-course preventive treatment regimens under the “1” include:

**1HP:** one month of isoniazid and rifapentine taken daily

**3HP:** once weekly isoniazid and rifapentine taken for three months

**3HR:** three months of daily isoniazid and rifampicin (specifically for kids)

Data from the 2023 World Health Organization (WHO) Global TB Report show how countries are scaling up access to the “1” regimens: between 2021 and 2022, there was a threefold increase in the number of people receiving rifamycin-based, short-course TB preventative treatment (TPT) regimens, and the number of countries offering these regimens increased from 52 to 74.<sup>1</sup> But universal access to TPT is a long way away, and universal access to short-course TPT is even further. Between 2018 and 2022, 15.5 million people received TPT – the majority of whom were people living with HIV.<sup>1</sup> This figure represents just over 50% of the target set by governments at the first United Nations High-Level Meeting on TB. And just 16% of those who received TPT in 2022 were provided with a “1” regimen.<sup>1</sup> Data from the 2023 Global Fund concept notes also indicate that while nearly all countries intend to scale up 3HP, implementation of 1HP remains much more limited.

### SPOTLIGHT

#### **3HP in Malawi: leadership from civil society proved instrumental**

*Interview with Edna Tembo (Coalition of Women Living with HIV and AIDS) and Kuzani Mbendera (National TB Program)*

TB prevention is a top priority for Malawi, given that nearly half of the individuals diagnosed with TB in the country are also living with HIV. With a donation from IMPAACT4TB and support from other partners, Malawi’s **TB and HIV programs worked together** to pilot 3HP in five districts accounting for 60% of newly diagnosed TB and HIV.

Using a combination of information sessions, trainings, and WhatsApp communications, civil society groups **supported healthcare workers** to administer the new regimen and **raised awareness among communities**, including traditional healers, to encourage uptake and adherence. Community leaders thoughtfully **addressed misconceptions** and fear of changes on both sides – for the providers and the people receiving TB preventive care. Issues with drug impurities

in the initial orders of 3HP made their communication efforts ever more important.

Malawi has reaped the benefits of this **community-driven** approach: uptake of 3HP among people living with HIV has increased year-on-year, and in 2022, 60% of people on antiretroviral therapy who received TPT received 3HP.<sup>2</sup> However, the lack of quality assurance laboratories remains an ongoing challenge.

Malawi’s 2020-2025 National HIV Strategic Plan has included 3HP as part of the TB prevention package, and with support from PEPFAR and the Global Fund, 3HP is being **scaled up nationally**. With the advent of a child-friendly formulation for 3HP, Malawi also plans to expand **access for children** under five years old and for HIV-negative people.

**“Make sure health workers are on your side. And choose the right people who will advocate and inform communities – they will be crucial for success.”** — Dr Mbendera

Many factors are enabling accelerated scale-up of short-course TPT. The recent reduction in the price of rifapentine brought the regimen cost of 3HP down to roughly \$10.<sup>3</sup> While 1HP continues to be priced at \$20, research has shown that both short-course regimens are cost-effective compared with longer TPT regimens.<sup>4</sup> The pill burden has also been addressed: the introduction of a fixed-dose combination (FDC) tablet of rifapentine/isoniazid shrank the pill burden of 3HP from nine to three pills per dose, and the recent development of a 300-mg rifapentine tablet brought down the pill burden of 1HP from five to three pills per dose. With three suppliers now in the market with quality-assured formulations — Lupin Limited, Macleods Pharmaceuticals, and Sanofi — rifapentine availability is expected to improve due to increased supply and competition between manufacturers.

While the provision of TPT among household contacts more than doubled between 2021 and 2022, the number of children under five receiving TPT has remained small and stagnant for the past five years.<sup>1,5</sup> In 2022, only 37% of these children received TPT despite being at high risk of progression to TB disease.<sup>6</sup> The recommendation of a long-awaited pediatric dispersible formulation of rifapentine by the Global Fund Expert Review Panel in 2023 will make it easier to offer 3HP to children; notably, the price of this product makes 3HP the cheapest TPT regimen for kids at any weight.<sup>7</sup>

## SPOTLIGHT

### 1HP in Zambia: cross-program collaboration was key to successful scale-up

*Interview with Dr Mubanga Angel (National TB Program) and Dr Patrick Lungu (former National TB Program)*

Following the WHO's recommendation of 1HP, Zambia took a strategic approach to updating its TPT guidelines, starting with **stakeholder consultations**. Key to Zambia's approach was close collaboration, including data sharing, between the HIV and TB programs. Whereas many countries leave TPT in the hands of the HIV program, contributing to poor access to the treatment among HIV-negative individuals, Zambia pushed TPT scale-up from the TB program.

**Open communication and transparency** were essential: stakeholders were encouraged to speak about their fears and concerns, which included potential side

effects and the risk of contributing to drug resistance. This approach helped win health workers' **trust and confidence**. As Dr Lungu put it, "it became a movement."

Zambia received a **catalytic investment** of 45,000 courses of 1HP through a donation from the Unitaid-funded IMPAACT4TB program for priority use among household contacts, prisoners, people with diabetes, people with silicosis, and transplant recipients. The National TB Program (NTP) actively **solicited feedback** from end-users — which was overwhelmingly positive — and within three months, they had begun rolling out 1HP in additional regions.

**"It is a win-win for both the patient and program. Patients want friendly, shorter, effective treatment; the NTP is interested in increasing TPT adherence. It is the right direction for TB and HIV programs to take together."** — Dr Angel



## The “4”: Drug-susceptible TB treatment

The short-course treatment regimens under the “4” include:

**4HPMZ:** four months of isoniazid, rifapentine, moxifloxacin, and pyrazinamide for the first two months

**4HRZE:** four months of isoniazid and rifampicin, with pyrazinamide (and ethambutol in certain settings) for the first two months (specifically for kids with nonsevere disease)

The WHO endorsement of 4HPMZ for adults and adolescents and 4HRZE for children with nonsevere disease in 2022 represented the first major advancement in drug-susceptible treatment in nearly half a century. Now it’s two years later and the “4” regimens remain vastly underutilized.

Our analysis of the Global Fund concept notes shows that at least seven countries – Azerbaijan, Bangladesh, Kenya, Liberia, Somalia, Thailand, and Vietnam – have interest in implementing 4HPMZ. The defining rate-limiting factor in the adoption of 4HPMZ is cost. As of March 2024, drug costs for 4HPMZ are over three times those of 6HRZE (US\$163 versus US\$46). Another barrier to implementing the “4” for adults is the daily pill burden, which goes from up to four pills a day with 6HRZE to up to nine pills a day with 4HPMZ.<sup>8</sup> However, quality-assured, three- and four-drug FDCs for 4HPMZ are expected to be available via the Global Drug Facility by the end of 2024, making the pill burden equivalent to 6HRZE. While it is unclear how the new FDCs will be priced initially, higher demand (and increased volumes) for 4HPMZ would likely lead to lower prices.

### SPOTLIGHT

#### 4HPMZ in Azerbaijan: reducing time spent on treatment helps meet people’s needs

*Interview with Dr Irada Akhundova (National TB Program) and Dr Aysel Ismayilova (Research Institute of Lung Diseases)*

Men ages 25-34 have the highest TB incidence in Azerbaijan. Pressured by the demands of work and supporting young families, these men **struggle to stick with and complete their TB treatment**. Incarcerated individuals, predominately men, are also a high-risk group for TB. The NTP saw switching to 4HPMZ and cutting the length of treatment by a third as an opportunity to **better meet the needs of people affected by TB**.

In 2024, Azerbaijan is **poised to offer the shorter four-month HPMZ** regimen for drug-susceptible TB to approximately 100 people in the general population and to continue to support 30 people’s 4HPMZ treatment in the

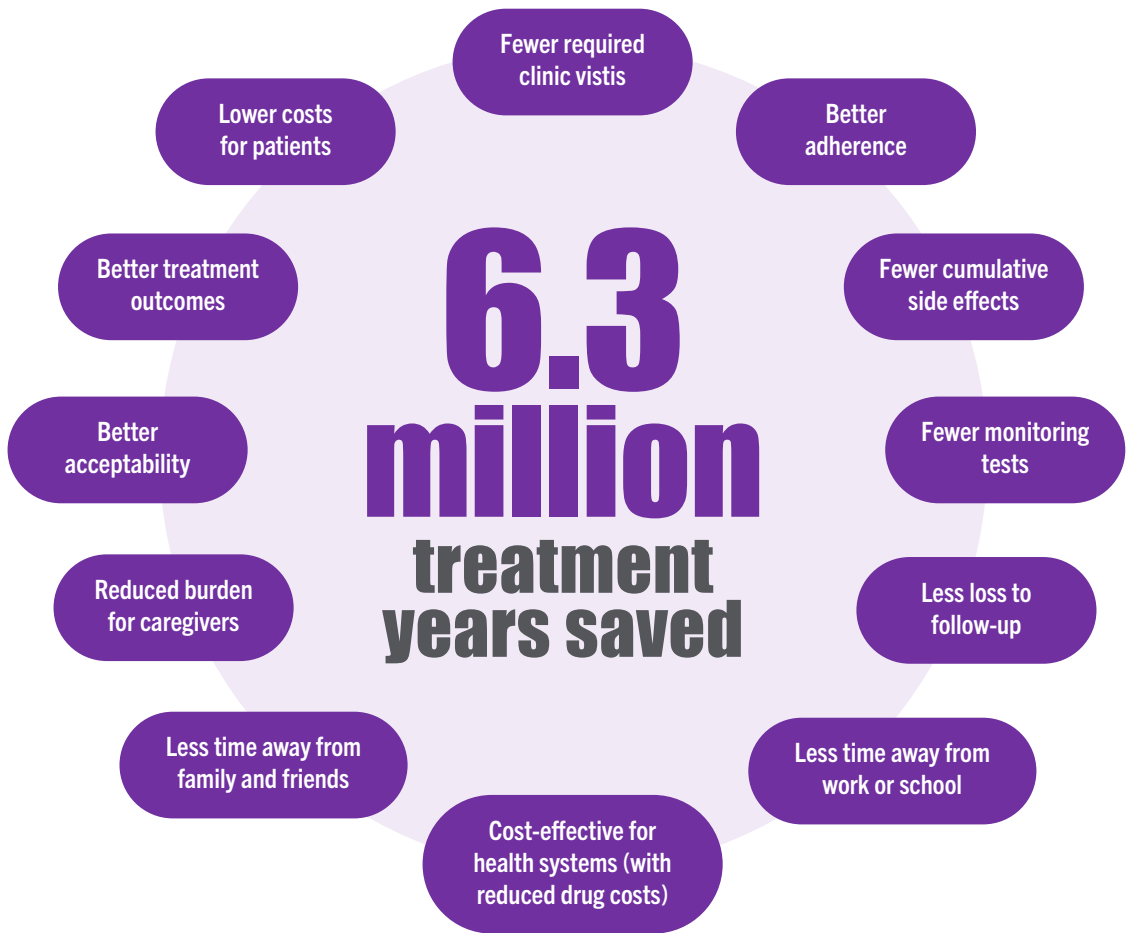
penitentiary system. Azerbaijan also plans to **expand provision of other shorter regimens** in 2024: 3HP for TB prevention and BPaL[M] for drug-resistant TB treatment.

Given the high incidence of drug-resistant TB in Azerbaijan, ensuring **adequate diagnosis** alongside the rollout of 4HPMZ is imperative. Currently, the country’s laboratory network consists of two reference laboratories for the civil and penitentiary sectors and five regional laboratories located throughout the country. These laboratories are equipped with a range of essential TB diagnostics, including Xpert MTB/RIF Ultra and Xpert MTB/XDR.

“Starting and doing is what will guide us – we will do our best to achieve desired results, stand by and treat our patients, and inspire others with our successes – but the most important thing is to start!” —Dr Akhundova

**FIGURE 2**

### Potential impact of implementing the four-month HPMZ regimen for drug-susceptible TB through 2030



Modeling suggests that switching all eligible adults from the six-month to the four-month regimen would result in the savings of 75.9 million months – that’s 6.3 million years – on TB treatment through 2030. This time saved on treatment could lead to significant savings for health systems and people receiving TB care. If all eligible people with TB in India, South Africa, and the Philippines alone received 4HPMZ in 2024, it is estimated that they would save a cumulative \$110 million in nonmedical expenses due to shorter duration of treatment (model assumptions described in annex 2).



Compared with 4HPMZ, scale-up of the “4” for children with nonsevere disease appears to be happening at a faster pace. 4HRZE is cheaper than the longer regimen, and the necessary quality-assured FDCs are already supplied. Our analysis of Global Fund concept notes shows that at least 25 countries have plans to scale up 4HRZE for treatment of nonsevere TB disease in children and adolescents. Unlike 4HPMZ, 4HRZE was included as a Global Fund program essential, which may partly explain its more rapid and wider adoption by NTPs.

WHO guidelines state that children under ten years of age who meet clinical criteria for nonsevere disease are eligible to receive the shorter regimen in the absence of chest X-ray or other tools for diagnosing nonsevere TB. While increasing access to chest X-ray is important for effective TB care more broadly, in the interim, clinical algorithms and monitoring are sufficient to scale up 4HRZE for children who stand to benefit from shortened treatment.<sup>5</sup>

## SPOTLIGHT

### 4HRZE in Kenya: a ripple of positive effects

*Interview with Dr Immaculate Kathure, Dr Nkirote Mwirigi, and Dr Farida Geteri of the National TB Program*

With children making up nearly 10% of its national TB burden, Kenya was motivated to introduce targeted programming for pediatric TB. Between 2022 and 2023, Kenya undertook a collaborative, strategic process to **update its national guidelines and diagnostic algorithms** to support the introduction of 4HRZE for children.

Substantial efforts were invested in reassuring providers that – based on strong clinical scoring criteria, a proper history and physical examination – a diagnosis of nonsevere disease can be made in the absence of a chest X-ray. The NTP **successfully piloted the policy changes** – including introducing the shorter regimen – in two counties. The initial introduction

of 4HRZE in Kenya has already generated a **ripple of positive effects** for TB-affected individuals, providers, and health systems. **Children have an easier time** completing treatment, and as a result, their families and caregivers are under less pressure. **Health system savings** from cutting children’s drug-susceptible treatment time by a third are now being reinvested in pediatric TB prevention and drug-resistant TB treatment.

Renewed political commitment has led to the **hiring of additional staff** – particularly to support commodity forecasting and procurement – and the appointment of a pediatric focal person within the ministry of health. National rollout of 4HRZE is currently underway.

“My advice to other countries is to champion children. Don’t be afraid to amend guidelines and diagnostic processes. Thanks to the changes we’ve implemented, we are expecting an increase in detection of pediatric TB and an improved treatment success rate.” — Dr Kathure



## The “6”: Drug-resistant TB treatment

The short-course regimens under the “6” include:

**6BPaL[M]**: six months of bedaquiline, pretomanid and linezolid, with moxifloxacin for fluoroquinolone-sensitive TB and without moxifloxacin for fluoroquinolone-resistant TB

Among the Global Fund concept notes analyzed, nearly 90% of countries included plans to scale up the six-month regimen to treat drug-resistant TB. The year-on-year increases in pretomanid procurement from the Global Drug Facility are indicative of progress and reflective of the change in WHO guidance between 2020 and 2022. In 2023, 55 countries ordered over 51,000 courses of pretomanid, representing a five-fold increase in the number of orders compared with 2022 when BPaL was only recommended by the WHO under operational research conditions. However, when compared with the burden of drug-resistant TB globally, access to BPaL[M] is still limited. An estimated 175,650 people were started on drug-resistant TB treatment in 2022 and, based on the Global Drug Facility procurement data, just 6% received BPaL[M].<sup>1</sup> In 2023, assuming a similar number of drug-resistant TB treatment starts, the proportion of people that received BPaL[M] increased to 29%.

### SPOTLIGHT

#### **BPaL[M] in Indonesia: highest-level political commitment accelerated rollout**

*Interview with Dr Tiara Pakasi of the National TB Program*

Encouraged by **political support** from the Minister of Health, the Indonesian NTP has rapidly accelerated the rollout of BPaL[M]. Following the WHO’s 2020 recommendation, Indonesia began conducting **operational research** on BPaL[M] supported by LIFT-TB. They achieved a treatment success rate of 97.9% with BPaL[M] – an outstanding improvement compared with their previous rate of 51%. Upon hearing the interim results, the Minister of Health called for urgent scale-up of the regimen.

Encouraging physicians to accept the new guidelines took regular webinars and **capacity-building** strategies, including site-visits and on-the-job training. With

the second largest gap in TB detection globally, expanding their **laboratory capacity** was a priority: they now have 2,200 GeneXpert machines that can run the test for rifampicin-resistant TB, which BPaL[M] treats. This includes 800 of the ten-color machines required to run the Xpert MTB/XDR cartridges required to rapidly test for resistance to moxifloxacin.

Supported by both **domestic and multilateral funding**, programmatic use of BPaL[M] is expanding nationwide. Indonesia is now turning its attention to introducing the four-month drug-susceptible TB regimens under operational research conditions.

“If I had to sum up the underpinnings of Indonesia’s successful rapid rollout of BPaL[M] in five words, they would be: leadership, determination, collaboration, communication, and monitoring.” — Dr Pakasi

The relatively rapid adoption of 6BPaL[M] in comparison to 4HMPZ, for example, is likely driven by several factors. In addition to being shorter, 6BPaL[M] has more pronounced safety and pill-burden benefits compared with existing standards of care. The drug costs are also less for BPaL[M] compared with the other regimens. At the time of the updated guideline release, the WHO launched the BPaLM Accelerator Platform to support implementation of the new regimens.<sup>9</sup> In addition, TB Alliance’s LIFT-TB and Fast Track the Cure programs, as well as Stop TB Partnership’s TB REACH initiative, have facilitated the adoption and scale-up of BPaL[M] through operational research supports, targeted advocacy, and service-delivery projects. Most significantly, persistent civil society advocacy paired with pricing negotiations brought the cost of bedaquiline down to \$130 per treatment course, or \$0.72 per day. Pricing negotiations also led to a 34% reduction in the cost of pretomanid. Yet, at \$240 per course, this single drug now constitutes more than half (56%) of the drug costs of the BPaL[M] regimen.

## SPOTLIGHT

### BPaL[M] in the Philippines: adoption facilitates decentralization of health services

*Interview with Dr Charisse Malbacias (Ministry of Health), Dr Nancy Rose Labarete (physician, private hospital), and Ms Louie Zepeda-Teng (TB People Philippines)*

Less than one year following the June 2020 WHO recommendation to implement BPaL[M] under operational research conditions, the Philippines initiated **operational research** on BPaL[M] supported by the LIFT-TB initiative.

The Philippines is undergoing major reforms to **decentralize health services**. The adoption of BPaL[M] – a shorter, simpler, safer regimen – is facilitating expanded access to people-centered drug-resistant TB treatment at the primary care level. This is especially important considering the number of affected people living in geographically isolated and mountainous areas. However, like Indonesia, the Philippines has a significant **gap in TB detection**, which, coupled with limited infrastructure for drug susceptibility

testing, threatens to limit the potential impact of BPaL[M].

Necessitated by the move to decentralize health services, the Philippines is investing heavily to **build capacity** of their TB program staff, with a particular focus on equipping them to **monitor for adverse events**. Highly trained staff will not only support BPaL[M] scale-up but also improve the quality of TB care more generally.

The NTP recognizes that effective partnerships, especially with affected communities, are essential to successfully change policies and introduce new regimens. Persistent **stigma and discrimination** against people with TB in the Philippines continue to be a barrier to engagement.

“Prioritizing community needs will be key to rolling out BPaL[M] countrywide. This includes providing communities with information and making sure social protection mechanisms are in place and fully funded. And civil society plays an important role to help advocate and make noise so all stakeholders in the country get behind scaling up the shorter, safer regimens.” — Ms Zepeda-Teng

The initial scale-up of 6BPaL[M] has already demonstrated major savings in treatment time for people receiving TB care and for TB programs. As of March 2024, in ten countries for which data were available, at least 2,773 people have already been enrolled on BPaL[M] either under operational research or routine programmatic conditions (Table 1). The number of BPaL[M] treatment starts across this sample of countries is small relative to the number of people eligible for the regimen, yet the impact of the switch is still dramatic. In comparison to an 18-month treatment regimen, each of those 2,773 individuals was spared a full year of their lives on treatment. From a programmatic perspective, that translates to the saved costs and efforts associated with at least 33,276 treatment months in these ten countries alone.

TABLE 1

### Treatment months saved from switching to BPaL[M] in ten countries

Country	Number of people on BPaL[M]	Treatment months saved (compared with 18-month regimen)
South Africa	1,181	14,172
Belarus	606	7,272
Uzbekistan	394	4,728
Pakistan	296	3,552
Sierra Leone	200	2,400
Democratic Republic of the Congo	36	432
Afghanistan	31	372
Russia	15	180
Tajikistan	9	108
Somalia	5	60

Source: Médecins Sans Frontières and National TB Programs.

### SPOTLIGHT

#### Ukraine and South Africa: innovative approaches to rapid policy adoption

Delivering access to the latest and best available TB technologies requires translation of WHO guidance into national policies. While this is necessarily a country-specific process, innovative approaches from Ukraine and South Africa stand out as **models that other countries could emulate** to adopt and roll out new TB tools more rapidly.

Even during armed conflict, **Ukraine** was one of the first countries to adopt policies to introduce and implement the 1/4/6 regimens.<sup>10</sup> Ukraine's innovative approach is to **directly adopt new WHO policy recommendations as national policies before going through the process of adapting them to the national context**. This stands out against the more common approach of countries taking time to adapt WHO

recommendations to the national context before updating national policies, which can delay the introduction of new tools.

**South Africa** continues to stay ahead of the curve on the adoption of new TB innovations. The country was one of the first to widely adopt Xpert MTB/RIF tests over a decade ago and more recently has pioneered early access to bedaquiline, delamanid, and pretomanid through Clinical Access Programs.<sup>11,12</sup> Rather than waiting for WHO guidance, South Africa **closely follows the science, anticipates the availability of new innovations, implements pilot studies, and begins adapting national policies accordingly** – sometimes before WHO recommendations are even issued.<sup>13</sup>





## Cross-cutting issues

To achieve 1/4/6x24, we need:

Greater inclusion of children and pregnant people in research on shorter, safer TB regimens

Universal access to diagnostics for TB disease, drug-resistance, and TB infection

### Children and pregnant people deserve better treatments, too

Two populations have, historically, been the last to benefit from scientific advancement in TB: children and pregnant people. Paradoxically, both populations are at higher risk for TB disease compared with their adult and nonpregnant counterparts.<sup>6</sup>

The SHINE trial, which showed that 4HRZE was noninferior to 6HRZE in children with nonsevere disease, was a pioneering study designed specifically around the needs of children.<sup>14</sup> And the WHO's rapid guideline update based on the trial's results showcased the potential impact of research centered on neglected and excluded groups.

At its launch, the 1/4/6x24 Campaign called for additional research to inform whether children – including those living with HIV – and pregnant people can safely take the suite of new shortened regimens. Since that call, there have been several studies designed to address remaining data gaps (see annex 4). And recent positive results from two key trials, endTB and BEAT-Tuberculosis South Africa, offer alternative short, all-oral regimens to treat drug-resistant TB in children and pregnant people.<sup>15</sup> Because the dosing and safety of pretomanid in children and pregnant people is still to be determined, countries should rapidly enable access to these pretomanid-sparing, shorter, all-oral regimens. Without access to the endTB and BEAT-Tuberculosis regimens, children and pregnant people will continue to be relegated to treatment with 9- to 11-month regimens with seven drugs or 18- to 20-month regimens with four to five drugs.

Family-centered approaches to care and resources for counselling and support remain vital, as does access to child-friendly formulations. Beyond therapeutics, more research and concerted action are urgently needed to close the diagnosis gap for children and pregnant people.<sup>16,17</sup>

### Access to better treatments demands better access to diagnostics

Ensuring all eligible people receive the best available shorter, safer regimens for TB prevention and treatment requires universal access to diagnostic testing for TB and drug resistance.<sup>18</sup>

#### Testing for TB disease

In 2022, 30% of the estimated 10.6 million people who developed TB disease – including more than 50% of children and adolescents – were not diagnosed or reported to NTPs.<sup>1</sup> Among those who were diagnosed, just 47% received a rapid molecular diagnostic as their initial test, as recommended by the WHO. The diagnostic gap for drug-resistant TB is even higher: an estimated 57% of people with drug-resistant TB were not properly diagnosed or linked to appropriate treatment in 2022.<sup>1</sup> Data from Global Fund concept notes indicate that all country programs have plans in place between 2024 and 2026 to increase access to rapid molecular diagnostics as the initial TB test. Countries such as Nigeria are leading the way in

scaling up access to rapid molecular testing. By significantly expanding the number of health facilities with rapid molecular testing instruments, Nigeria more than doubled TB notifications between 2019 and 2022.<sup>19-21</sup> However, funding the scale-up of rapid molecular testing remains a major challenge with significant gaps between country needs and ambition versus available domestic and Global Fund resources.

Non-sputum-based tests currently in the research and development pipeline, such as tongue swab-based molecular tests and next-generation urine LAM tests, could prove essential to closing TB testing gaps. Even with reduced sensitivity, non-sputum-based tests are expected to result in a higher overall number of people diagnosed with TB by increasing the number of people who can provide a sample.<sup>22,23</sup> For pediatric TB, use of non-sputum samples such as stool are already recommended for rapid molecular testing and should be universally implemented as a sampling option to improve pediatric TB diagnosis.<sup>24</sup>

### **Testing for drug-resistance**

Data from Global Fund concept notes indicate that most country programs have plans in place between 2024 and 2026 to scale up access to decentralized rapid molecular drug-susceptibility testing for resistance to rifampicin, isoniazid, and the fluoroquinolones. Because 4HPMZ brings the fluoroquinolones (i.e., moxifloxacin) into first-line treatment for drug-susceptible TB, decentralized access to fluoroquinolone resistance testing is essential. However, data from the Global Fund concept notes indicate that only about one in three countries plan to test for fluoroquinolone and isoniazid resistance among all people diagnosed with TB. The remainder either did not specify or limited fluoroquinolone and isoniazid resistance testing to people with diagnosed rifampicin resistance, an approach primarily directed at determining eligibility for drug-resistant TB regimens, such as BPaL[M]. Greater country-level transparency on implementation of rapid molecular tests for TB detection and drug susceptibility testing is needed to better assess gaps and progress.<sup>25</sup>

### **Testing for TB infection**

Testing for TB infection prior to initiating TPT is not required for high-risk groups. As such, a lack of access to TB infection tests should not preclude scale up of the “1” regimens among people living with HIV and children under five years old who are household contacts of a person with TB. Increasing access to testing for TB infection, however, can help target interventions to scale up the “1” regimens among household contacts five years of age and older who are not living with HIV. Data from the Stop TB Partnership’s 2023 Step Up for TB Report indicates that 85% of countries that responded to the survey (17/20) have policies in place to scale up access to TB infection testing among this population.<sup>26</sup> But only 30% of these countries have plans to use next-generation skin tests, which are expected to be significantly less expensive compared to interferon-gamma release assays with comparable accuracy.<sup>26,27</sup>



## Achieving 1/4/6x24: a collective call to action

The 1/4/6 Campaign calls on key stakeholders to take the following urgent and concrete actions to put in place the staff, stuff, space, systems, and support necessary for everyone, everywhere to have access to the 1/4/6 regimens before the end of 2024.

### Country governments

At the 2023 United Nations High-Level Meeting on TB, country governments pledged to ensure that at least 90% of people with or at risk of TB are reached with quality prevention, diagnosis, and treatment by 2027.<sup>28</sup> To deliver on this commitment, country governments also pledged to invest \$22 billion a year in global investments by 2027, nearly four times the level of global investment in 2022.<sup>1</sup> Meanwhile, an analysis of country proposals to the Global Fund shows a funding gap of \$1.1 billion between country ambition and available funding due to insufficient investments by donor countries in the Global Fund and insufficient domestic investment in TB programs.<sup>19</sup> Inadequate financing from donor countries contributes to an accelerated transition for high-burden countries from multilateral to domestic financing for TB drug procurement, known as the “procurement cliff,” introducing significant risk for countries in establishing reliable, quality supply chains. Country governments must urgently increase levels of multilateral and domestic financing for TB services necessary to close these gaps and put in place the full healthcare infrastructure – the staff, stuff, space, systems, and support – necessary for delivering access to the shorter 1/4/6 regimens.

#### CALL TO ACTION

- All donor countries must significantly increase investments in multilateral and bilateral TB financing.
- All high-TB-burden countries must announce major increases in domestic funding for TB to support the universal rollout of the best diagnostics and regimens for TB prevention and treatment.

### World Health Organization

At the 1/4/6x24 Campaign commitments meeting in 2022, the WHO committed to facilitating dialogue among ministries of health, technical partners, donors, and all relevant stakeholders to address implementation barriers for the 1/4/6 regimens and share best practices. Since then, progress on introducing and scaling up the four-month regimens for drug-susceptible TB has been slow, despite the potential impact shorter treatment could have on millions of eligible people each year. The WHO has taken concrete, commendable action to track uptake and promote access to the “1” regimens for TB prevention and the “6” regimens for drug-resistant TB, including through the BPAL[M] Accelerator. The WHO should take similar action for all newly recommended regimens, including the “4” regimens for drug-susceptible TB.

#### CALL TO ACTION

Facilitate dialogue among countries and other stakeholders on introducing and rolling out the four-month regimens and actively track and promote uptake of these regimens.

## Stop TB Partnership

The Stop TB Partnership has been a crucial partner for members of community and civil society in providing information and resources to support advocacy for person-centered care, access to the best available TB technologies, and increased domestic investments in the TB response.

### CALL TO ACTION

**Provide more resources and support to civil society to implement country-level accountability initiatives to:**

- **Track country program implementation of the 1/4/6 regimens and supportive diagnostics as well as the provision of food, housing, counselling, and other psychosocial services for people to fully recover from TB; and**
- **Advocate for their governments to increase domestic investments in the TB response to meet commitments made at the 2023 United Nations High Level Meeting on TB.**

## Global Fund to Fight AIDS, Tuberculosis and Malaria

At the 1/4/6x24 Campaign commitments meeting in 2022, the Global Fund pledged to use its \$2 billion annual purchasing power to ensure drugs in the 1/4/6 regimens and supportive diagnostics are available at affordable prices and are scaled up to deliver impact. The growing demand from countries to begin implementing 4HPMZ for drug-susceptible TB in adults and the impending availability of new FDCs and rapid diagnostics for TB detection and drug susceptibility testing present clear opportunities for the Global Fund to use its purchasing power and other levers available through its next generation market shaping strategy to address market barriers to the introduction of the four-month regimen and new diagnostics. Meanwhile, poorly planned and inadequately resourced transitions to domestic financing and procurement have resulted in some countries reverting to the use of older regimens, procuring drugs that are not quality assured, ceasing to use pediatric formulations, and facing catastrophic drug stockouts (as was the case in India and Kenya in 2023).<sup>29,30</sup> It is critical that the Global Fund also address risks associated with countries' transition to domestic funding for TB procurement.

### CALL TO ACTION

- **Catalyze uptake of 4HPMZ by initially covering more expensive drug costs and to use Global Fund's market-shaping power to secure more affordable prices for 4HPMZ;**
- **Work with WHO and other stakeholders to sensitize country programs to new diagnostics and to understand how they should be optimally positioned to serve country program needs and priorities;**
- **Based on country needs and priorities, use Global Fund's market-shaping power to secure more affordable prices for new diagnostics;**
- **Implement risk assessments for countries transitioning to domestic funding; and**
- **Maintain Global Fund support until effective domestic systems of procurement with reliable, quality supply chains are in place.**



## United States Agency for International Development

As high-burden countries transition from receiving funding from the Global Fund to the use of domestic funding for TB services, many face challenges in establishing reliable, safe, and effective supply of quality medicines. USAID can support countries in building capacity to adopt and implement key policies and roll out new tools.

### CALL TO ACTION

- 
- Support countries through technology transfer, technical assistance, and capacity strengthening to improve program quality and active TB drug-safety monitoring and management (aDSM); and
  - Leverage USAID resources to increase domestic financing for TB and improve sustainable supply of quality TB commodities at affordable prices, including those in the 1/4/6 regimens.

## Unitaid

The Unitaid-funded IMPAACT4TB project to expand access to short-course rifapentine-based TPT resulted in over 4 million courses of 3HP and 1HP procured in 2022, compared with 35,000 in 2017.<sup>31</sup> Unitaid's market-shaping work on rifapentine should be extended to address barriers to the uptake of 4HPMZ.


### CALL TO ACTION

- 
- Coordinate and synergize with other actors, including the Global Fund and the Global Drug Facility, on a market-shaping strategy for 4HPMZ;
  - Make investments that will help shape the market for 4HPMZ and catalyze uptake of the regimen; and
  - Issue a call for proposals to support policy advocacy and demand generation work necessary to accelerate the introduction and scale-up of the regimen.

## MedAccess

MedAccess develops innovative financing partnerships with pharmaceutical and diagnostics manufacturers to reduce prices and support introduction of new health products. MedAccess negotiated volume guarantees that helped to reduce the prices of rifapentine in 2021 and pretomanid in 2022.<sup>32,33</sup>

### CALL TO ACTION



Use a country- and stakeholder-driven approach to identify opportunities to deploy MedAccess' market shaping tools to accelerate access to new TB diagnostics necessary to close diagnostic gaps and support the scale-up of the 1/4/6 regimens.

## TB research funders

There is an unacceptable delay between when TB innovations are available generally versus when children and pregnant people can benefit from them. Research assessing the safety and pharmacokinetics of pretomanid and 4HPMZ for these populations is particularly imperative. Some of the necessary studies – such as RADIANT Moms Plus to evaluate 4HPMZ in pregnant people – have been designed but remain unfunded.

### CALL TO ACTION



**Advance and open enrollment for studies evaluating the safety and dosing of the 1/4/6 regimens in children and pregnant people.**

## Danaher/Cepheid

Due to the high price of Xpert tests and limited funding, countries remain constrained from fully scaling up access to rapid molecular testing in accordance with WHO recommendations. Nigeria, for example, plans to sharply increase testing countrywide, but only a portion of the costs are covered by domestic and Global Fund resources.<sup>19</sup> The situation is the same in most high-burden low- and middle-income countries. The 20% price reduction of Xpert MTB/RIF Ultra in 2023 to \$7.97 is a positive step that is expected to save \$30 million per year allowing the procurement of 3.6 million additional test cartridges. Even with the price reduction and related savings, high-burden countries cannot afford to implement these tests at the required scale. And the Xpert MTB/XDR test remains profoundly overpriced at \$14.90 per test.<sup>34</sup>

### CALL TO ACTION



**Price Xpert TB tests based on the transparent, publicly verifiable cost of production, in accordance with demands from the Time for \$5 Campaign.**

## Otsuka/Viatrix:

Delamanid – a powerful new medicine for drug-resistant TB – is a key component of shorter treatment regimens, especially for children and pregnant people who are currently unable to benefit from access to BPaL[M]. Yet, delamanid remains inaccessible due to exorbitant pricing. Otsuka markets the drug at \$198 per person per month and Viatrix at \$207 per person per month, but evidence shows generic versions of the drug could be sold as low as \$5-16 per person per month (based on volumes amounting to 108,000 treatment courses yearly).<sup>35</sup> Despite the primary patent on delamanid expiring in October 2023, generic manufacturers are expected to be delayed in entering the market, including the market for children, in part because of their inability to obtain Otsuka's delamanid for use as a reference product.<sup>36</sup>

### CALL TO ACTION



**Substantially reduce the price of delamanid. Otsuka must also:**

- **Enable generic manufacturers to enter the market by supplying the reference products and withdrawing all remaining patents on delamanid; and**
- **Reduce the price of the pediatric dispersible formulation of delamanid, given its essential role in enabling children to be able to benefit from access to better regimens.**

## **Annex 1. List of Campaign coalition members**

African Coalition on TB (ACT)

Asia Pacific Counsel of AIDS Service Organizations (APCASO)

Global Coalition of TB Advocates (GCTA)

Global TB Community Advisory Board (TB CAB)

Lean on Me Foundation

Médecins Sans Frontières (MSF)

O'Neill Institute for National and Global Health Law at Georgetown University

Partners In Health (PIH)

Results Canada

SMART4TB Consortium

Stop TB Partnership

Survivors Against TB

TB Europe Coalition (TBEC)

TBPPM Learning Network

TB Women Global

The Sentinel Project Against Pediatric Drug-Resistant TB

Treatment Action Campaign (TAC)

Treatment Action Group (TAG)

We Are TB

Wote Youth Development Projects Community Based Organization

Zambia Association for Prevention of HIV and TB (ZAPHIT)

## Annex 2. Methods

This report analyzes progress in the scale-up of the 1/4/6 regimens. The analysis was informed by and cross-checked between various data sources.

The primary data source was funding requests to the Global Fund that reflect planned implementation during the current three-year grant cycle (2023-2025). The concept notes from 37 countries were analyzed using keyword searches related to the 1/4/6 regimens and diagnostics. The search terms were: 1HP, 3HP, 3HR, short, HPMZ, HRZE, 4-month, 4 month, four-month, four month, BPaL, rapid molecular, initial, GeneXpert, Truenat, XDR, fluoroquinolone, FQ, LPA, line probe assay. This analysis has several limitations. It does not capture domestic or other investment in the scale-up of the 1/4/6 regimens; nor does it capture whether countries' requests to the Global Fund will be fully funded. The full results from the Global Fund concept note analysis are included in annex 3.

Other data sources include the Stop TB Partnership's 2023 Step Up for TB Report tracking TB policy adoption, the 2023 WHO Global TB Report, Stop TB Partnership's Global Drug Facility, Médecins Sans Frontières, and NTPs. The data and narratives presented in the case studies were collected via open-ended interviews with NTPs and members of civil society conducted by Petra Heitkamp and supported by Asgar Ismayilov.

The modeling work referenced in the section on 4HPMZ was conducted by Tess Ryckman (Johns Hopkins University). The modeling estimates the cumulative difference in months spent on treatment among adults with rifampicin-susceptible pulmonary TB through 2030 if all eligible people globally, starting at the beginning of 2024, were to initiate 4HPMZ instead of 6HRZE. The projections relied on several assumptions. The trends in the number of adults treated for pulmonary rifampicin-susceptible TB were assumed to return to pre-COVID levels, with gradual incremental improvements in the case detection ratio and stable proportions of rifampicin-susceptible TB that is fluoroquinolone resistant.<sup>1</sup> Based on drug resistance surveillance studies, the proportion of rifampicin-susceptible TB that is fluoroquinolone resistant in 2024 was assumed to be 10% in Pakistan; 5% in India, Bangladesh, and Nepal; 3% in China; and 1% in all other countries.<sup>37-47</sup>

The modeling estimates of savings to people receiving TB care included savings on out-of-pocket nonmedical expenditures associated with treatment (e.g., transportation to clinics and supplementary food) as well as reductions in lost wages due to time spent in care (i.e., attending treatment visits). These estimates were taken from an ingredients-based costing analysis that was conducted for the 2023 *Lancet Commission on TB* report.<sup>48</sup> See that report (particularly appendix page 20) for a more detailed method description. Nonmedical patient-borne costs under the standard of care were based on references 49 through 52.<sup>49-52</sup> Costs were estimated in 2021 U.S. dollars.

### Annex 3. Review of 2023 funding requests to the Global Fund

These data represent planned implementation of the 1/4/6 regimens and supportive diagnostics within the GC7 grant cycle (2023-2025). The limitations of these data are detailed in the methods section (see annex 2).

	"1"			"4"		"6"	Rapid molecular diagnostics as initial test		Fluoroquinolone resistance testing	
	1HP	3HP	3HR	4HPMZ	4HRZE	BPaL[M]	GeneXpert	Truenat	Xpert MTB/XDR	FQ LPA
Azerbaijan	No	Yes	No	Yes	No	Yes	Yes	No	Yes	Yes
Bangladesh	No	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	No
Cameroon	Yes	Yes	No	No	Yes	No	Yes	Yes	Yes	Yes
Central African Republic	No	Yes	No	No	Yes	No	Yes	Yes	No	Yes
Congo	No	No	Yes	No	Yes	Yes	Yes	Yes	No	Yes
Côte d'Ivoire	No	Yes	No	No	Yes	No	Yes	No	Yes	No
Democratic Republic of the Congo	No	Yes	Yes	No	Yes	Yes	Yes	No	Yes	Yes
Eswatini	No	Yes	Yes	No	Yes	Yes	Yes	No	Yes	Yes
Ethiopia	No	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	No
Ghana	No	Yes	Yes	No	Yes	Yes	Yes	No	Yes	Yes
Guinea	No	Yes	Yes	No	No	Yes	Yes	No	Yes	Yes
Guinea-Bissau	No	Yes	No	No	Yes	Yes	Yes	No	Yes	No
India	No*	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes
Indonesia	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes
Kenya	No	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Kyrgyzstan	No	Yes	No	No**	No	Yes	Yes	No	Yes	Yes
Lesotho	No	Yes	Yes	No	Yes	Yes	Yes	No	Yes	No
Liberia	No	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes
Malawi	No	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes
Mongolia	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	No
Mozambique	No	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes
Myanmar	No	Yes	No	No	No	Yes	Yes	Yes	Yes	Yes
Namibia	No	Yes	Yes	No	No	Yes	Yes	No	Yes	Yes
Nigeria	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes
Pakistan	No	Yes	Yes	No	Yes	Yes	Yes	No	Yes	No
Philippines	No	Yes	Yes	No	Yes	Yes	Yes	No	Yes	Yes
Republic of Moldova	Yes	Yes	No	No	Yes	Yes	Yes	No	Yes	Yes
Sierra Leone	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes
Somalia	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Tajikistan	Yes	Yes	No	No	No	Yes	Yes	No	Yes	Yes
Thailand	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes
Uganda	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	No
Ukraine	Yes	Yes	Yes	No***	Yes	Yes	Yes	No	Yes	Yes
United Republic of Tanzania	No	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes
Viet Nam	No	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Zambia	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes
Zimbabwe	No	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes

\* India received 20,000 1HP patient courses donated from IMPAACT4TB.

\*\* Kyrgyzstan reported a policy on 4HPMZ implementation in Stop TB Partnership's Step Up For TB 2023 survey.

\*\*\* Ukraine procured 4HPMZ according to data from the Global Drug Facility.

## Annex 4. Advancing research on the 1/4/6 regimens for neglected populations

Priorities	Progress
<b>The “1”</b>	
<p>Ensure <b>people and children living with HIV</b> can safely take rifapentine-based TPT with ARVs</p> <p>Ensure <b>younger adolescents and children</b> can safely take rifapentine-based TB preventive treatment</p>	<p><b>TBTC Study 35</b> is investigating the pharmacokinetics, safety, and tolerability of 3HP in children with or without HIV (results expected in 2024).</p> <p><b>DOLPHIN Kids</b> is investigating the safety, tolerability, and drug-drug interactions of 3HP among children and adolescents living with HIV (results expected in 2026).</p> <p><b>IMPAACT 2024</b> is investigating the dosing, pharmacokinetics, safety, tolerability, and drug-drug interactions of 1HP in children with or without HIV (enrollment anticipated in 2024).</p> <p><b>ACTG 5372</b> is investigating whether once-daily dosing of dolutegravir is safe and sufficient when given with 1HP for treatment of TB infection (results expected in 2025).</p> <p>A new <b>child-friendly formulation</b> of rifapentine was developed to improve the palatability of rifapentine-based regimens for children.</p>
<p>Ensure <b>pregnant people</b> can safely take rifapentine-based TPT</p>	<p><b>DOLPHIN Moms</b> is evaluating the safety, tolerability, and drug-drug interactions of 1HP and 3HP in pregnant people with HIV (results expected in 2025).</p>
<p>Evaluate preferences and needs of the target populations to see what they want and will use</p>	<p><b>‘One To Three’</b> (in South Africa, Mozambique, and Indonesia), <b>Ultra Corto</b> (in Brazil), and <b>The HIV Netherlands Australia Thailand Research Collaboration</b> trial (in Thailand) are all comparing 1HP to 3HP and will provide insight on relative safety, adherence, and tolerability.</p>
<b>The “4”</b>	
<p>Ensure <b>younger adolescents and children</b> can safely take the 4-month HPMZ regimen</p>	<p><b>RADIANT Kids</b> is proposing to evaluate the safety, pharmacokinetics, and tolerability of 4HPMZ in children (protocol in development).</p> <p><b>SMILE-TB</b> will compare 2HPMZ to 4HRZE or 6HRZE in children, investigating how both regimens affect the levels of dolutegravir in the body (enrollment anticipated in 2024).</p> <p>Note: <b>ACTG 5406</b> is investigating whether twice-daily dosing of dolutegravir is safe and sufficient when given with 4HPMZ for drug-susceptible TB treatment in adults (currently enrolling).</p>
<p>Ensure pregnant people can safely take the 4-month HPMZ regimen</p>	<p><b>RADIANT Moms Plus</b> is proposing to investigate the safety and pharmacokinetics of 4HPMZ in pregnant people (concept in development).</p>
<p>Evaluate risk factors or populations that would benefit from treatment extensions</p>	<p><b>SPECTRA-TB</b> is proposing to identify populations that would benefit from a shorter duration of HPMZ (protocol in development).</p>
<p>Evaluate preferences and needs of the target populations to see what they want and will use</p>	<p><b>SMILE-TB</b>, set to compare 2HPMZ to 4HRZE or 6HRZE, will also explore how children and caregivers think and feel about taking TB medicines.</p> <p><b>RADIANT Kids and RADIANT Moms Plus</b>, set to evaluate 4HPMZ in children and pregnant people, respectively, will also include qualitative substudies on acceptability.</p>

Priorities	Progress
The “6”	
Optimize shorter regimens for younger adolescents, children, and pregnant people	<p><b>endTB</b> evaluated five new nine-month all-oral regimens and found three of the regimens to be noninferior to the standard of care, providing a suite of new options suitable for children and pregnant people (results presented at 2023 Union Conference).</p> <p><b>BEAT-Tuberculosis South Africa</b> evaluated a six-month all-oral delamanid-containing regimen; the trial included children and pregnant women (results presented at 2023 Union Conference).</p> <p><b>PRISM-TB</b> will investigate the safety and efficacy of different durations of BPaL[M] using a stratified medicine approach. Adolescents <math>\geq 14</math> years old, PLHIV, and pregnant and lactating people will be eligible for enrollment (protocol in development).</p> <p><b>IMPAACT 2020</b> will investigate the safety and efficacy of six-month all-oral regimens among children <math>\leq 15</math> years old living with or without HIV (protocol in development).</p> <p><b>PRISM-Kids</b> will investigate the safety and efficacy of four- and six-month regimens of bedaquiline, delamanid, linezolid, and levofloxacin (BDLL) and six months of bedaquiline, delamanid, clofazimine, and linezolid (BDCL) in children <math>\leq 14</math> years old with drug-resistant TB (protocol in development).</p> <p><b>IMPAACT 2005</b> will investigate the pharmacokinetics, safety, and tolerability of delamanid in children with multidrug-resistant TB (currently enrolling).</p>
Further optimize the dose and duration of linezolid	<p><b>PRISM-TB, PRISM-Kids, and IMPAACT 2020</b> are likely to provide insight into linezolid duration optimization for adults and children.</p>
Evaluate preferences and needs of the target populations to see what they want and will use	<p><b>IMPAACT 2020</b> will enroll parents and caregivers along with their child to assess acceptability, priorities, and preferences for drug-resistant treatment.</p> <p><b>BENEFIT KIDS</b> is conducting taste-masking and acceptability evaluations to support the development of child-friendly formulations of drug-resistant TB medications.</p>
Ensure younger adolescents, children, and pregnant people can safely take pretomanid-containing regimens	<p><b>IMPAACT 2034</b> is investigating the safety, tolerability, and acceptability of a single dose of pretomanid in infants, children, and adolescents living with or without HIV (currently enrolling).</p>
Evaluate risk factors or populations that would benefit from treatment extensions	<p><b>PRISM-TB</b> will investigate the safety and efficacy of different durations of BPaL[M] using a stratified medicine approach.</p>

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